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BIOLOGICAL PSYCHIATRY

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PSYCHOLOGY TEACHERS UPDATE

Psychology Teachers Update is designed to give a brief overview of the main developments in the different areas of psychology. There is a proliferation of journals and research, and it is very difficult to keep abreast of the latest trends, particularly in the many and varied areas of psychology.

Each issue of Psychology Teachers Update will cover a particular topic, and summarise the main research directions and findings in the last ten to fifteen years approximately. The aim is to give teachers the feel of what is happening in that area of psychology.

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Introduction

The medical or biomedical model has dominated, in recent years, the field of mental health. This is primarily the treatment of mental illness as the same as physical illness. The latest variation on the medical model is known as "biological psychiatry".

This is "a technical term that denotes physiological and biochemical approaches to psychiatric aetiology and ..excludes psychosocial approaches" (Gelder 1996 p401). Thus the emphasis is upon physiological, biochemical, and genetic explanations as opposed to social or psychological causes of mental illness. In some ways, biological psychiatry is a hardening of the medical model.

Gelder (1996), in his review of the state of biological psychiatry, admits that there are three problems which must be addressed:

i) The cause of the mental problem may be remote in time. For example, early childhood may be the cause of adult mental disorders, but direct biological evidence is limited. However, there is indirect evidence.

The absence of gliosis ⁽¹⁾ in certain areas of the brain suggests pre- and post-natal brain problems, and the link to adult schizophrenia (Bruton et al 1990).

ii) One cause may have several effects. For example, a single gene that causes Huntington's chorea is also associated with bipolar disorder (Peyser and Folstein 1993).

iii) One effect may have several causes. There will be predisposing, precipitating and maintaining factors for a particular mental disorder. It is also accepted that there will be the interaction of genetic and biochemical factors with psychological and social ones.

For example, Kendler et al (1993a), from the Roscommon family study, see the liability to current major depressive disorder due to recent stressful life events, a genetic predisposition, a previous history of major depressive disorder, and neuroticism. They estimate that 60% of the cause is due to genetics and 40% due to stress and neurochemistry.

In such situations, it is necessary to make judgments (speculations even) about indirect relationships between physiological processes and causation.

Two key developments over the last few years have

aided the growth of biological psychiatry:

a) The increasing sophistication of technology to study the brain; ie: scanning techniques (or neuroimaging).

b) The increased knowledge of human genetics, as highlighted by the ongoing "Human Genome Project" (sometimes called molecular genetics).

Thus there is a proliferation of studies and information about mental disorders using these techniques. For example, Vastag (2002) reviews the latest research on depression, and the dysfunctional metabolism and blood flow in the brain's emotional areas. Also irreversible changes in brain structure due to the depression, and deficiency in serotonin receptors in the amygdala and hippocampus, among other areas.

Biological psychiatry is a very technical area with much ongoing research at the moment. The aim of this issue of Psychology Teachers Update is to outline the methods being used, and give a flavour of the research findings. It is not possible to be comprehensive in a short booklet. Liddle (2001) is the most thorough recent book on neuroimaging, and Nurnberger and Berrettini (1998) for genetics.

Brain Scanning Techniques

Brain scans can be used in a number of ways:

i) To study the biochemistry in the brain. This can involve a number of processes:

a) The action of neurotransmitters through the binding of molecules (in vivo receptor binding) with PET scans.

b) The measurement of brain receptor populations in different illnesses; eg: the study of striatal dopamine D2 receptors in drug-naïve schizophrenia sufferers.

But with PET and SPECT scans, different radioactive tracers do find different results (eg: ^{11}C -N-methylspiperone versus ^{11}C raclopride) (Grasby et al 1996).

c) Receptor occupancy and tissue pharmacokinetics (2) of psychotropics; eg: understanding different neuroleptics and dopamine D1 receptor activity.

d) Functional effects of drug-induced neurotransmitter manipulation. Vaidya and Duman (2001) explain how anti-depressants work in depression. Major, recurrent depression is seen as linked to hippocampus damage. Anti-depressants reverse this trend by increasing the growth and survival of BDNF (brain-derived neurotrophic factor). This means the continued plasticity of neural pathways which are lost in depression.

Depression may arise when neuronal symptoms do not exhibit appropriate, adaptive plasticity in response to external stimuli such as stress...Anti-depressant treatments may exert their therapeutic effects by either reversing this dysfunction or by independently stimulating an adaptive neuronal plasticity within the system (Vaidya and Duman 2001 p62).

ii) For the measurement of cerebral blood flow; eg: the use of water proton signals with MRI scans.

More specifically, regional blood flow (rCBF) to particular areas of the cortex can be measured. PET scans show a time lag of 1-3 seconds for blood flow rises after the start of activity in an area of the brain where there is low rCBF.

iii) Closely linked to (ii) is the measurement of cerebral metabolism; eg: the rate of use of oxygen or accumulation of deoxyglucose shows the active parts of the brain in PET scans. It is possible now to study

regional glucose metabolism (rCMRglu) in specific areas of the cortex, using, for example, 18 F-deoxyglucose (18-FDG).

iv) To assess structural brain differences; eg: the reduction in certain brain areas in CAT scans.

Most PET scan experiments use neuropsychology challenge studies; ie: specific tasks to perform for both control and experimental group, so that the active brain can be compared.

COMPUTERISED AXIAL TOMOGRAPHY (CAT SCANS)

First used in 1972 (Sadock and Sadock 2003), this method produces a 3D X-ray picture of the static brain based on many X-rays from different angles and then combined together by the computer.

X-ray machines are based on the principle that abnormal tissue absorbs X-rays to different degree to normal tissue. It is best at showing the presence of blood clots, tumours, and enlarged ventricles.

There is a small risk from the X-rays if CAT scans are used too often on the same individuals.

Owens et al (1985) performed a British study based on a sample of 112 hospitalised patients with schizophrenia. CAT scan results showed that lateral ventricular size increased more often in the patients than controls. In other words, the brain volume was reduced. The type of treatment was found to play no role either. These findings were constant over the length of the illness suggesting it was not a product of the disorder (Lewis 1996).

This method has been supplanted by others, except for assessing calcification, which may be invisible on MRI (Sadock and Sadock 2003).

POSITRON EMISSION TOMOGRAPHY (PET SCANS)

This technique is able to show the active brain by following the movement of a radioactive substance that has been injected into the brain. Radioactively labelled glucose molecules travel to active areas of the brain. When the radioactive atoms decay, they emit positrons (sub-atomic particles). These encounter electrons (the opposite type of particles) and both are annihilated. This gives rise to gamma rays that travel in opposite directions, and these can be traced to the point of origin (3).

Its strength is the ability to show blood flow patterns in the brain, which can be affected by, for example, strokes.

Different radioactive tracers (eg water labelled with oxygen isotope ^{15}O) can be used to target different aspects of the brain's activities, like blood flow, glucose metabolism, dopamine receptors, or MAO activity (Grasby et al 1996).

Because a small amount of radioactivity is involved, the World Health Organisation recommends one PET Scan per five years. 10 PET scans or 2 SPECT scans are the same as annual background radiation exposure (Liddle 1996).

Baxter et al (1992) performed a study based upon 18 patients with obsessive-compulsive disorder given either drug therapy or behaviour therapy. Initial PET Scans showed high levels of activity in the caudate nucleus in the right hemisphere when suffering an attack of the disorder.

Thirteen of the patients responded to the treatment, and, in a second PET scan, the caudate nucleus was less active.

Single-photon emission computed tomography (SPECT)

This is a more sensitive measure of blood flow in the brain. It makes use of exametazime labelled with technetium isotope, $^{133\text{m}}\text{Tc}$, for example (Liddle 1996).

NUCLEAR MAGNETIC RESONANCE IMAGING (NMRI or MRI)

This technique, which entered clinical practice in 1982 (Sadock and Sadock 2003), also shows the static brain, through the use of magnetic fields.

It works by measuring the hydrogen atoms in water. The hydrogen nuclei are exposed to strong magnetic fields and line up like tiny magnets. Then they are hit with radio signals which causes them to move out of alignment. This produces a signal that can be measured.

Compared with CAT scans, MRI provides a better contrast between grey and white matter. The upshot of which is more anatomical detail (Johnstone 1993).

This is no need for radioactive substance to be injected, but there is concern about the effect of the strong magnetic field on the body.

Johnstone et al (1989) had three groups of participants receive MRI scans: 21 individuals with schizophrenia, 20 with bipolar disorder, and 21 controls.

The first group showed two brain structure differences compared to the others: larger temporal horns of the lateral ventricles, and a reduction in the left temporal lobe area.

Johnstone (1993) summarises the other 8 MRI studies of schizophrenia to that point (table 1).

	STUDIES SHOWING DIFFERENCES	STUDIES SHOWING NO DIFFERENCES
NUMBER OF STUDIES	6	2
TOTAL PATIENTS	169	36
TOTAL CONTROLS WITH OTHER MENTAL DISORDERS	20 bipolar	0
TOTAL HEALTHY CONTROLS	125	16

(After Johnstone 1993)

Table 1 - Summary of results of 8 MRI studies on schizophrenia.

While Lewis (1996) summarises the evidence from seven studies between 1992-5 showing the decrease in the volume of cortical grey matter among patients with schizophrenia. Five of the studies found significant differences. In total, there were 234 patients, 247 controls with no mental disorders, and, in two studies, 53 controls with bipolar disorder. The average reduction in volume was at least 4%.

Reduced temporal lobe volume in schizophrenia has been confirmed most recently by Lawrie et al (2002).

Concerning another disorder, anti-social personality disorder, Raine et al (2000) found reduced prefrontal grey matter among those scoring high on PCL-R (4). But the reduced volume was not in a specific part of the frontal cortex (Blair 2003). The frontal cortex is seen as linked to planning, moral thinking, and impulse control. Behaviours that sufferers of anti-social personality disorder are traditionally poor at.

MAGNETIC RESONANCE SPECTROSCOPY (MRS)

MRS is based on the same principles as MRI, and uses magnetic fields - unpaired photons and neutrons aligned with a magnetic field. Radio frequency pulsing causes nuclei to absorb and emit energy. This produces a spectrum of the brain's chemical compounds.

There are different types of MRS: for example,

observing the proton nucleus (^1H) in the hydrogen atom (H MRS), or the stable isotope of phosphorous (^{31}P) (Frangou and Williams 1996) ⁽⁵⁾.

Frangou and Williams (1996) quote studies using H MRS which find conflicting results concerning changes in N-acetyl aspartate (NAA) in patients with schizophrenia. A reduction in NAA is seen as linked to less brain volume.

While Dager et al (1994) used this specific method to study increased brain lactate levels in unmedicated panic disorder - before, during and after the attack. Volunteers were asked to try and induce a panic attack while being scanned. Increased lactate levels are linked to glucose metabolism in the absence of oxygen. In other words, a shortage of oxygen may be involved in inducing the panic attack.

An alternative molecule to use with MRS is ^{31}P (isotope of phosphorous). It is possible to measure the energy utilisation of the brain when biochemical processes are working. For example, the measurement of phosphomonoesters (PME) precursors of membrane phospholipids, and phosphodiesteres (PDE) that breakdown the product of above. This provides information about neuronal membrane metabolism.

A number of replicated studies have found reduced PME levels and increased PDE levels in the prefrontal cortex in first episode drug naive patients with schizophrenia (Frangou and Williams 1996). In other words, there is a physical change in cell processes in these individuals. These changes are also found in normal ageing. Could schizophrenia be a case of premature ageing at the cell or molecule level of the brain (Frangou and Williams 1996)?

Another use of MRS is to investigate the pharmacokinetics ⁽²⁾ of psychotropic (psychiatric) drugs. The actual pharmacological effect on the brain of psychotropics has to be estimated from blood (serum) levels, for example, and is far from perfectly accurate.

Renshaw and Wicklund (1988) found with MRS that brain lithium concentration was half that in the blood measurements. In other words, less of the drug was reaching the area of the body that mattered (ie: the brain) despite circulating in the blood. This may be due to the molecules of the drug being unable to cross the brain-blood barrier.

Likewise, the use of MRS has shown that it takes six months of steady use of fluoxetine (anti-depressant) to reach maximum concentration in the brain (which is twenty times the serum concentration) (Sadock and Sadock 2003).

FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

This technique detects tissue mass based on blood flow, by measuring changes in deoxyhaemoglobin when neurons are active. Increased neural activity means a reduction in the concentration of deoxyhaemoglobin. In practice, it is possible to localise neuronal activity.

There is no need for a radioactive tracer (Liddle 1996). But acquisition of enough images for study can require the participant's head to remain still in the machine for up to three hours. Small changes in head position can lead to "erroneous interpretations" of brain activation (Sadock and Sadock 2003).

Functional MRI is also used with "perfusion imaging", which attempts to detect certain isotopes. But there is uncertainty about the relationship between perfusion, metabolism, and neuronal activity (Goodwin 1996).

Goodwin (1996) summarises 24 studies (five using perfusion imaging) with fMRI showing correlations between major and unipolar depression and reduced cerebral activity (both global and specific). This gives a total of 566 patients and 528 controls. Ten of the studies found significant differences. Six of the studies showed a significant negative correlation between less global functioning and Hamilton Rating Scale for Depression (HRSD) score ⁽⁶⁾.

Three studies showed the relationship between the frontal cortex and HDRS, and one study with the temporal cortex. One interpretation of these findings is linked to the integration of emotional experiences, or lack of it in depression. This is further explored in Phillips (2003).

Smith et al (2002) have used fMRI to show a persistent abnormality in cerebellar responses in women recovering from major depressive disorder. The patient group showed less response in the cerebellum during anticipation of a noxious stimulus. The researchers argue that this could be a vulnerability marker of liability to recurrent depression.

A recent fMRI study (Wykes et al 2002) has shown increased brain activation in the frontocortical areas, associated with working memory, in patients with schizophrenia who received successful cognitive remediation therapy (CRT) ⁽⁷⁾.

MAGNETOENCEPHALOGRAPHY (MEG)

This technique makes use of changes in the magnetic

fields in cortical neurons, which can be detected by magnets placed on the scalp. Liquid helium coiled superconducting sensors (eg: single superconducting quantum inference devices; SQUIDS) are used to pick up the faint magnetic fields. It is able to detect changes in signals over milliseconds, but it does not have the localised accuracy of MRI scans.

OVERVIEW OF BRAIN SCANNING

From time to time, there are review articles of neuroimaging studies, like Hull (2002) for Post-Traumatic Stress Disorder (PTSD). This review located studies since August 2001 on brain structure and function in PTSD (table 2).

Though most of the studies find changes in the sufferers of PTSD, the findings are not necessarily the same.

METHOD	NUMBER OF STUDIES	TOTAL PATIENTS	TOTAL CONTROLS	FINDINGS
CAT	2	24	0	both find change in brain structure eg: ventricular brain ratio (VBR)
MRI	8	187	193	6 studies show change eg: hippocampus volume
fMRI/MRS	3	36	23	all show change in brain function eg: exaggerated automatic amygdala response to threat
PET	10	82	83	all show change in brain function eg: increased rCBF in orbitofrontal cortex
SPECT	4	55	91	all show different change in brain functions

(After Hull 2002)

Table 2 - Summary of neuroimaging studies of Post-Traumatic Stress Disorder.

Schizophrenia and Biological Psychiatry

There is much application of neuroimaging techniques to the study of schizophrenia. The techniques of biological psychiatry are highlighting the "subtle brain abnormalities" in schizophrenia (Liddle 1996). Research with scanning techniques are confirming a number of findings.

1. Hypofrontality

A diminished rCBF in the frontal lobe relative to the posterior in patients with schizophrenia. The opposite is found for controls without schizophrenia (Liddle 1996). This can account for the "psychomotor poverty syndrome" (see below).

But not all patients at all phases of the illness show these differences in rCBF (Early et al 1987). Furthermore, it:

..must be emphasized that these changes in structure and function are very subtle and that there is no way a person can be "diagnosed" as suffering from schizophrenia simply by examining brain scans (McCreadie 2000 p15).

2. Symptoms and cerebral blood flow patterns

The symptoms of schizophrenia have been grouped together based on common physiological changes or "syndromes" (Liddle 1987) (table 3):

i) "Psychomotor poverty syndrome" - poverty of speech, flat affect (eg: unchanging facial expressive), and decreased spontaneous movement associated with catatonic versions of the disorder. These symptoms are sometimes called "negative symptoms", while the other two syndromes are closer to "positive symptoms" (Crow 1985).

ii) "Disorganised syndrome" - thought form disorders, distractibility, and inappropriate emotions.

iii) "Reality distortion syndrome" - delusions (eg: persecution), and hallucinations.

SYNDROME	AREAS OF BRAIN SHOWING INCREASES IN rCBF	AREAS OF BRAIN SHOWING DECREASES
psychomotor poverty syndrome	basal ganglia	bilateral frontal/ left parietal cortex
disorganised syndrome	right anterior cingulate cortex and adjacent medial prefrontal cortex; thalamus	right ventrolateral frontal cortex: bilateral parietal cortex
reality distortion syndrome	medial temporal lobe; left lateral frontal lobe; ventral stratum	posterior cingulate; left lateral temporal cortex and adjacent parietal cortex

(After Liddle 2001)

Table 3 - Syndromes of schizophrenia and cerebral blood flow patterns (8).

3. Evidence from neuropsychological studies

Neuropsychological studies assess cerebral activity while participants are carrying out specific cognitive tasks. The Wisconsin Card Sorting Test (WCST) (Berg 1948) is commonly used. This involves the sorting of cards showing different shapes and colours, and demands problem-solving skills.

For example, Berman et al (1992) compared MZ twins, where one suffered from schizophrenia, on this task. There was less prefrontal cortex activation in the co-twins with schizophrenia while card-sorting.

It is also possible to focus upon specific symptoms, like auditory hallucinations. McGuire et al (1995) compared patients with schizophrenia with and without auditory hallucinations, and controls without the disorder. The task for the participants while in the scanner was to imagine sentences spoken in another's voice. The different pattern of brain activity in those with schizophrenia who experienced auditory hallucinations is believed to be linked to the areas of the brain that monitor inner speech (table 4).

ACTIVATED AREAS OF BRAIN	CONTROLS	PATIENTS WITH WITH AUDITORY HALLUCINATIONS	SCHIZOPHRENIA WITHOUT AUDITORY HALLUCINATIONS
left frontal gyrus	yes	yes	yes
supplementary motor area	yes	yes	no
left middle temporal gyrus	yes	yes	no

(After Liddle 1996)

Table 4 - Differences in brain activation based on experiencing auditory hallucinations or not.

Other research has suggested that the symptoms of schizophrenia may be problems with connections between cerebral areas rather than differences at specific sites (Liddle 1996).

4. Establishing causality

CAT and MRI studies have shown that brain abnormalities are present at the onset of the disorder and remain constant (ie: non-progressive).

This would suggest evidence for a genetic basis to these abnormalities, but these abnormalities may be combined with "early environmental insults", like birth complications: "a totally genetic explanation for schizophrenia is untenable and that environmental factors must be involved" (Frangou and Murray 1996 p593).

The key abnormalities are ventricular enlargement, and reduced whole brain volume and cortical grey matter. There is evidence of ventricular enlargement in well relatives of those with schizophrenia, and also in unaffected co-twins of MZ pairs.

It is possible to see schizophrenia (and these brain abnormalities) as a developmental condition. There are five lines of evidence used to back up this view (Frangou and Murray 1996):

i) No degeneration during illness.

ii) Absence of gliosis in post-mortems (1).

iii) Pre-morbid abnormalities; eg: minor physical anomalies (MPAS). This means that there is evidence of subtle motor, linguistic and social deficits in children

who develop schizophrenia as adults. Jones et al (1994) report such findings in a British cohort of 4746 individuals born one week in March 1946.

iv) Subtle neurological abnormalities.

v) Social and cognitive deficits.

If schizophrenia is a developmental condition based on an interaction of a genetic disposition and early environmental factors, how does the illness take its course? Two possibilities are proposed - known as the early or late "lesion" hypotheses.

a) Early "lesion" hypothesis - The "lesion" (or brain damage) in foetal life interacts with normal neurodevelopment to produce the symptoms of schizophrenia in adulthood. The trigger to the development of schizophrenia is the normal selective synaptic pruning at adolescence (Weinberger 1987).

b) Late "lesion" hypothesis - The focus is upon the deviation in maturational processes that occur in the brain during adolescence. The main evidence comes from the increasing deterioration in cognition during childhood (Feinberg 1982).

But both explanations are unclear about the nature of the "lesion" (ie: the actual physiological processes) (Frangou and Murray 1996). The debate is updated in Cotter and Pariante (2002).

5. Physical illness and mental illness

One viewpoint being taken is to see schizophrenia as similar to diabetes (insulin-dependent diabetes mellitus; IDDM). In particular, the fact that there are different types of IDDM:

It is known that one subtype of diabetes is caused by a single, point mutation in the insulin gene.., another is strongly genetic and has a late age of onset. A third type is less strongly genetic, has an early age of onset.. Eventually ..we may learn that schizophrenia is composed of different genetic and biological subtypes
(Gurling et al 1991 pp106-107).

Kaufmann et al (1996) take the analogue further: both illnesses have an unknown mode of inheritance which is not a single gene, and there are varying symptoms, and age of onset.

The development of genetic models of mental disorders show the closer link to physical illness being made in biological psychiatry.

Genetics

The study of genetics (or "psychiatric genetics") comes under the new term "genetic epidemiology". This is "a science that deals with the aetiology, distribution, and control of disease in groups of relatives, and with inherited causes of disease in populations" (Morton and Chung 1978). The aim is to predict the "laws" of transmission of genes for complex syndromes (Sham 1996).

It is accepted that single genes will not be the sole explanation of mental disorders ⁽⁹⁾, so the search is for patterns of genes which produce an illness. Traditional methods like twin and adoption studies are used, as well as family studies, and the newer molecule genetic techniques relating to DNA sequencing.

This section of the booklet will be divided into two parts: (i) traditional methods for establishing the genetic basis of behaviour, and (ii) molecular genetic techniques.

TRADITIONAL METHODS FOR STUDYING INHERITANCE

Family studies

Nurnberger and Berrettini (1998) feel that family studies can answer three questions:

1. Is the phenomena found more frequently among the blood relatives of an affected individual compared to relatives or controls? That is, are relatives of an affected subject at increased risk for the disorder compared to relatives of control subjects?
2. What other phenomena (possibly genetically related) are also found more frequently among relatives of an affected individual? That is, what other disorders may share a common genetic vulnerability with the phenomenon in question?
3. Can a specific mode of inheritance be discerned? (pp9-10).

This type of study is based around the "genetic family tree" of sufferers. Working with a sufferer (proband) ⁽¹⁰⁾ of a particular mental disorder, the researchers try to discover how many "first degree relatives" (eg: mother, father, siblings) also have the same (or similar) mental disorder. A few of the studies use control groups.

The risk for the disorder can be calculated as the "relative risk" (Nurnberger and Berrettini 1998):

$$\text{Relative risk} = \frac{\text{Risk for relatives of affected probands}}{\text{Risk for relatives of controls}}$$

Table 5 gives a summary of some recent family studies.

STUDY	COUNTRY	PROBAND	FIRST DEGREE RELATIVES	MAIN FINDINGS
Andreasen et al (1987)	USA	616 affective disorder	2423	probands with bipolar disorder, 5.8% relatives suffered
McGuffin et al (1988)	UK*	83 depression	not known	increased risk of depression, not due to life events
Merikanges et al (1994)	?	133 major depression 82 control	1331	common basis to alcoholism, anxiety, and depression
Jones et al (1993)	UK*	195 "functional psychosis"	891	female and early onset sufferers had more relatives than male or late onset sufferers
Maier et al (1993)	?	525 schizophrenia/ schizoaffective/ bipolar disorder/ major depressive disorder 64 alcoholism 109 control	2070	familial links in schizophrenia and schizoaffective; schizoaffective and bipolar disorder; not schizophrenia and bipolar disorder**

(* both studies in Camberwell, South London)

(** supports view that schizophrenia and affective disorder opposite ends of continuum; Kendler et al 1993b)

(After Sham 1996)

Table 5 - Summary of findings of some family studies.

Twin studies

This method has been used for many years to establish the inherited component of behaviours. The main focus has been monozygotic (MZ) twins reared apart compared to dizygotic (DZ) twins reared together. The differences in the concordance rates were seen as the inherited component.

There is always a problem finding enough MZ twins reared apart (Brewer 2002), so the current interest is simply a comparison of the MZ and DZ concordance rates.

The environment is assumed to be equal (Sham 1996).

Twin studies are used for three reasons today:

i) To establish the genetic overlap between different syndromes.

Kendler et al (1987) found evidence of a "genetic distress" that is a combination of both anxiety and depression. The statistical techniques used produced a common genetic origin (technically a 30% loading) for these two disorders among over 3000 pairs of twins.

While Kendler et al (1995), using the Virginia Twin Register of female pairs (1033 pairs), have found shared genetic factors for major depressive disorder and generalised anxiety disorder, and for phobia, panic disorder and bulimia.

ii) To show the continuity of genetic factors at different stages of an illness.

Kendler et al (1993b) again using the Virginia Twin Register on two separate occasions, one year apart, found that genes accounted for approximately 50% of liability for major depressive disorder on both occasions.

iii) To find the relationship between genetic and mediating or environment factors in the development of an illness.

It is possible to build models to explain the basis of mental disorders. Kendler et al (1993c) studied the development of major depressive disorder and adverse life events over one year with the same sample as Kendler et al (1993b). From their statistical analysis, the researchers produced a three layer model (which accounted for 50% of variance) of the causes of major depressive disorder:

- distal layer: genetics; parental warmth and childhood parental loss;
- intermediate layer: neuroticism; lifetime trauma; past depression;
- proximal layer: social support; recent difficulties; recent stressful life events.

Using twin studies in this way has led to attempts to produce heritability estimates for mental disorders - eg: schizophrenia 68% (Kendler 1983); bipolar disorder 59% (Bertelen et al 1977) ⁽¹¹⁾.

All of the uses of twin studies today are combined with statistical techniques developed in biometrics. For example, structured equation modelling (SEM), which gives a pattern of predicted correlations that are compared to the findings (eg: Clifford et al 1984).

Adoption studies

This method is still used in a similar way to the past (Brewer 2002). Researchers find sufferers of the particular disorder who were adopted, and then discover how many biological and adopted relatives also had the same disorder.

There are accepted problems with the use of this method (Sham 1996):

- i) no assumption can be made of equal environment between adoptees and control, nor between adopted and biological family environments;
- ii) the sample of adoptees are not representative of the general population;
- iii) age of adoption is key.

One of the best known and extensive adoption studies comes from Copenhagen (Kety et al 1983).

Using the detailed adoption records kept in the Danish Population Register, the researchers looked for children adopted young, who were born between 1924-47 in Copenhagen. There were 5483 child adopted by non-relatives in this period. The researchers found 507 in this group who had been hospitalised with schizophrenia, and chose 33 to study.

A matched control group of 33 was also established. Then the researchers hunted for details of the biological relatives, and whether any of them had been diagnosed with schizophrenia (chronic, acute or borderline), uncertain schizophrenia or inadequate personality.

Four hundred and sixty-three biological relatives of the 66 studied individuals were found and their names checked on the psychiatric registers. This study used only documents.

A rate of 8.7% was found for the schizophrenic adoptees group. This is 13 of the 150 biological relatives: 7 were definite schizophrenia, 4 uncertain, and 2 inadequate personality. This compared to 1.7% for the control group (ie: 2 individuals).

Joseph (2001) criticises the broad definitions used in this study, among other problems.

The Copenhagen study has been extended to the whole of Denmark (Kety et al 1994). The biological relatives of adoptees with schizophrenia (22/342) showed the disorder more than adopted parents or controls.

The whole sample has been rediagnosed with DSMIII-R criteria (Kendler et al 1994) (table 6).

RELATIVES	FIRST DEGREE	SECOND DEGREE
ADOPTES WITH SCHIZOPHRENIA	16/68	14/141
CONTROLS	5/107	4/192

(After Sham 1996)

Table 6 - Numbers of those diagnosed with schizophrenia in Kendler et al (1994).

MOLECULAR GENETIC APPROACHES

The "Human Genome Project" has created a real enthusiasm for finding genetic answers to questions about behaviour:

When finally interpreted, the genetic messages encoded within our DNA molecules will provide the ultimate answers to the chemical underpinnings of human existence...but will also explain, at the chemical level, the role of genetic factors in a multitude of diseases, such as ...schizophrenia.. (Watson 1990 p44).

The molecular genetic approaches which have developed with the increasing knowledge of genes are based around the sequencing of DNA. This is the establishing of the role of specific genes, and the search for differences or patterns of them in diseases.

The common technique currently used is positional cloning ⁽¹²⁾. "Libraries" of DNA can be searched as part of "physical mapping". These are multiple copies of DNA used for sequencing and naming.

Any genes identified as relevant are examined in patients and controls to establish the mutation that causes the illness. However, when a genetic marker is identified as inherited exactly as a trait, it is assumed that the genetic mutation lies within one million bases ⁽¹³⁾ of the marker. Still like searching for that needle, but in a small haystack (Sadock and Sadock 2003).

Kaufmann et al (1996) distinguish three types of

genetic study:

i) Clinical genetics studies a specific (clinical) population with a "genetic bottleneck" (ie: there are a limited number of ancestors and thus access points for the disease genes to the population); eg: bipolar disorder among "Old Order Amish" in USA (Egeland et al 1987).

ii) Molecular genetics attempts to identify the regions of the chromosome involved.

iii) Statistical genetics employs complex statistical analysis to demonstrate inheritance patterns.

A well-established finding using this molecular genetic approaches is the mutation in the Presenilin-1 gene on chromosome 14 in families with a particular type of Alzheimers (known as "autosomal dominant familial" Alzheimers) (Sherrington et al 1995).

GENETIC MECHANISMS

Most diseases are complex and not linked to single genes. There are a number of genetic mechanisms involved (Craddock and Owen 1996):

i) Epistasis - this is the interaction of multiple genes to produce the illness; eg: schizophrenia (Risch 1990). This process is known to be the cause of retinitis pigmentosa (progressive degeneration of the retina) (Craddock and Owen 1996).

ii) Locus heterogeneity - this is where multiple genes are involved, but any one gene can produce the illness on its own also; eg: schizophrenia (McGuffin et al 1994). Retinitis pigmentosa is linked to 14 different loci (gene positions) (Craddock and Owen 1996).

iii) Allelic heterogeneity - there are multiple alleles ⁽¹⁴⁾ at a single disease locus. This is a number of possible genes at one particular situation, and a certain combination produces the illness; eg: bipolar disorder (Sandkuyt and Ott 1989).

iv) Dynamic mutation - here at a single disease locus, the allele mutates between generations. A particular gene mutates between parents and offspring; eg: schizophrenia (Bassett and Honer 1994). This is the case for Huntington's chorea.

v) Parent of origin effect - the expression of the

allele depends upon the parental origin. The gene at a particular locus from the biological father will have a different effect to that from their biological mother; eg: bipolar disorder and maternal transmission (McMahon et al 1995).

The absence of maternal chromosome 15 (q11-13) leads to Angelman syndrome (eg: spasms, "puppet-like" movements, and low intelligence), while absence of the paternal version causes Prader-Willi syndrome (which includes the symptoms of obesity and low intelligence) (Craddock and Owen 1996).

vi) Mitochondrial gene mutation - the illness is linked to the maternal pattern of inheritance as genes in the mitochondria ⁽¹⁵⁾ are only inherited from the mother; eg: bipolar disorder (McMahon et al 1995). This mechanism may be involved in some forms of deafness (Craddock and Owen 1996).

Molecular genetic approaches make use of linkage studies, association studies, and animal models.

Linkage studies

This technique attempts to infer the relative position of genes on the chromosome between parents and offspring based on the "genetic parameters" known from Human Genome Project. There is a tendency for two different genes on the same chromosome to remain together during inheritance. But this linkage can be broken by, for example, chromosomal mutation and the new combination of genes.

If the offspring develop a disorder, which the biological parents do not have, simplistically it could be the mutation that causes the disorder. Linkage studies make use of a large family and statistical tests to detect the significance of shared allele, or use affected sibling-pair analysis ⁽¹⁶⁾.

The technique of linkage studies makes use of the locus of "marker allele"; ie: genes always known to be in particular places on the chromosome (eg: "candidate gene" and colour blindness). The allele is the alternative forms of a particular locus (position of the gene); ie: one possible version from each parent. Each biological parent gives a unique nucleotide sequence for that particular gene position. It is possible to work backwards to see which parent has given the particular gene to the offspring.

Clerget-Darpoux (1991) notes three variations in the statistics used with linkage studies: the parametric

method, multi-point mapping, and non-parametric methods. The technical use, and problems of linkage studies are discussed in Edwards (1991).

Linkage studies have found various genes on particular chromosomes involved in mental disorders (table 7).

EVIDENCE	STRONG	MODERATE	WEAK
BIPOLAR DISORDER	X (Xq26-28)* 4; 18(p11)*	21 (q21)*	6; 11
SCHIZOPHRENIA	6	22	5
ALZHEIMERS	21;14		

(* numbers in brackets are specific positions on chromosome).

(After Sham 1996; Nurnberger and Berrettini 1998)

Table 7 - Examples of chromosomes found in linkage studies for three mental disorders.

Association studies

This technique seeks to compare the combination of certain alleles for a particular gene to the frequency in the general population. This can be done in two ways:

a) by the comparison of "marker genotypes" (combinations of genes) in unrelated patients and unrelated controls;

b) by the comparison in patients and their biological parents.

Association and linkage studies make use of complex statistical analysis, for example, "quantitative trait loci" (QTL) (Craddock and Owen 1996). This type of analysis is most useful in polygenic situations to try to establish the importance of individual genes. This records gene influence scores on a continuous scale rather than the categorical scale of affected/unaffected.

Association studies have found strong evidence for Alzheimers disease and the Apolipoprotein E (ApoE) allele on chromosome 19 (Hardy 1995), and a negative association between the low activity form of ALDH2 (aldehyde-dehydrogenase-class2) on chromosome 17 with alcoholism (Sham 1996).

Use of animal models

The information on specific genes can be complimented by studies to show the genes "in action" in non-human animals. This is usually done in two ways:

i) Selective breeding - once a particular genes have been implicated, it is possible to bred animals known to have that particular gene to see the outcome in future generations. For example, Hann and Edwards (1994) bred rats with susceptibility to "learned helplessness".

ii) Transgenic studies - these involve the introduction of cloned human genes into non-human animals to see the effect. Games et al (1995) did this with a mutation in the amyloid precursor protein gene on chromosome 21 (linked to Alzheimers) into mice.

Footnotes

1. Gliosis is a process that relates to glial cells that hold neurons together and provide nutrients. It is also linked to biochemistry.
2. Pharmacokinetics refers to the drug's passage through the body. This includes the concentration at the site of action as determined by the drug's absorption, distribution, biotransformation (breakdown of the active elements of drug), and excretion through the body (Whalley 1993). The mode of delivery (eg: oral) also influences this process.
3. Technical aspects of this process, including fluid-attenuated inversion recovery (FLAIR), in Sadock and Sadock (2003).
4. The PCL-R (Psychopathy Checklist-Revised) (Hare 1991) is a commonly used 20 item scale for measuring psychopathy.
5. Full details of the nuclei available in Sadock and Sadock (2003).
6. The Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960; 1967) measures the severity of depression in an unstructured interview based around 17 items originally. It is commonly used in psychiatry and clinical psychology.
7. Cognitive remediation therapy (CRT) focuses on practising three executive functions (cognitive flexibility, working memory, and planning) (Wykes et al 1999) to help overcome cognitive difficulties in mental disorders.
8. It is interesting how findings are changing very quickly. Here is a copy (table 8) of the same as table 3 based on Liddle et al (1992). Often the studies use very small samples which limits generalisation of the findings. This process can be helped by replication.

SYNDROME	AREAS OF BRAIN SHOWING INCREASES IN rCBF	AREAS OF BRAIN SHOWING DECREASES
psychomotor poverty syndrome	caudate nucleus - both sides	prefrontal/parietal cortex - left side
disorganised syndrome	anterior cingulate cortex	right ventral prefrontal cortex; contiguous insula
reality distortion syndrome	left medial temporal lobe; left lateral frontal lobe (near Broca's area)	posterior cingulate; left lateral temporal lobe and adjacent parietal cortex

(After Liddle et al 1992)

Table 8 - Syndromes of schizophrenia and cerebral blood flow patterns in 1992.

9. The idea that a single gene is the cause of a problem is known as "Mendelian transmission" (Whatley and Owen 1991).

10. Probands are "affected persons or index cases" (Gelder et al 1996).

11. A common way of estimating heritability is Holzinger's Index (Nurnberger and Berrettini 1998):

$$\text{Heritability} = \frac{\% \text{ MZ concordance} - \% \text{ DZ concordance}}{100 - \% \text{ DZ concordance}}$$

12. "Positional cloning" is "the capacity to identify disease genes by virtue of their physical location within the genome" (Kaufmann et al 1996 p6). Details of this process in "psychiatric genetics" in the same reference.

13. DNA (deoxyribonucleic acid) is made up of four nucleotide bases: adenine (A), guanine (G), cytosine (C), and thymine (T).

14. At any given genetic locus, each individual carries two copies (alleles) of the DNA sequence which defines that locus. One of these alleles is inherited from the mother and the other from the father. These alleles will be transmitted with equal probability (that is, $\frac{1}{2}$), one of the two alleles to each offspring. If two genetic loci are found "close" to each other on a chromosome, their alleles tend to be inherited together (not independently) and they are known as linked loci (Nurnberger and Berrettini 1998 pp13-14).

15. Genes are mostly located inside cell nuclei, but a small number of genes are within the mitochondria of the cells (Bentley 1999).

16. Affected sib-pair analysis (Suarez and van Erdeewegh 1978) is used when a disorder is rare. It relies on fact that siblings share 50% of their genes by chance. Any shared alleles with greater than 50% probability are of interest (Nurnberger and Berrettini 1998).

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